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Clinical Proceedings

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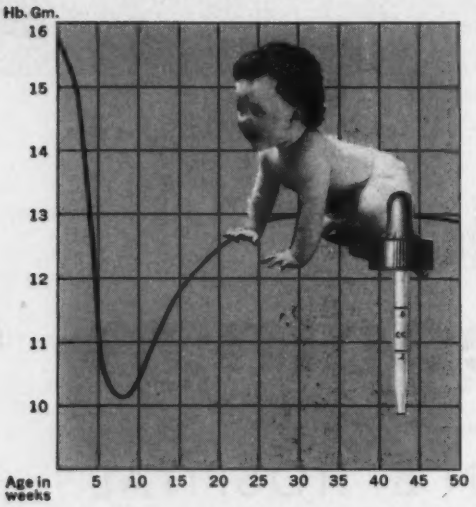

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(1) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86: 553, 1954. (2) Smith, C. H.: Bull. New York Acad. Med. 30: 155, 1954. (3) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1: 375, 1953. (4) Sturgeon, P.: Pediatrics 13: 107, 1954.

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OBESITY AND COLORED STRIAE IN ADOLESCENCE*

With a Testimonial to Dr. Joseph S. Wall

Warren R. Sisson, M.D.†

On this occasion we, the friends of Dr. Joseph S. Wall, have an opportunity to renew our loyalty to him and again measure his impact upon our lives and on the field of pediatrics. His life and deeds will always accent his claim for an established spot in our hearts and minds. He was a great humanitarian devoted to the youth of this city and our country, and he dedicated himself to helping all children have a fuller, happier, and more healthful life.

My association with Dr. Wall was not one of great intimacy in private life, but rather one that evolved because of a common interest, a similar objective. Like a great river formed by the conjunction of many tributaries, his life incorporated the lives of many others to make an enthusiastic group for better child care.

Although I had known Joe Wall for many years, about ten years ago, when he was president of the American Academy of Pediatrics, he asked me to be responsible for the Study of Child Health Services in the United States. Dr. Wall's interest in this investigation and his guidance can never be accurately assayed, but his influence determined directly or indirectly the success of this project. My part in this study was the direct result of Dr. Wall's friendship. His high ideals, his intelligence, his friendship, and his loyalty have enriched and inspired my life as they have the lives of many in this audience, and our gratitude can be expressed by our presence here today, to re-dedicate this auditorium with his friends.

It would be of interest to know what the real challenge of Dr. Wall's life would be if he were with us today. He had many facets to his character: he could have succeeded in many fields of endeavor. He could have been solely a teacher or an administrator, but as one tries to analyze the motivating forces in his life, we see that he required a more substantial challenge, and this he found in the ills to which man is heir. In his early medical experience he must have been greatly troubled by the toll taken, especially among children, by diseases such as typhoid, the acute digestive diseases of infancy, diphtheria, and rickets, to mention only a few. He clearly saw that the children of this nation are its greatest asset, a fact that some people high in office even today seem to forget or to be unaware of.

* The first Joseph S. Wall lecture given in the Children's Hospital in Washington, D. C., May 21, 1955.

† Forsyth Dental Infirmary for Children, Boston, Massachusetts.

Although many or most of the diseases which probably first interested Dr. Wall in the field of pediatrics have surrendered, I believe that he would still find the greatest challenge to his intellect in the study of youth, in some of its phases and in some of its failures to adjust to our culture.

* * * * *

It is the plan of this discussion to present purely clinical observations of some of the changes that take place in boys and girls during the period of development which culminates with maturity. This period is commonly called adolescence. Many of the remarks, while they are based upon personal observations, are in no way new, but a reiteration of accepted findings.

The physical characteristics of this period may be divided into those signs which are regarded as obligatory, or typical, and those that are non-obligatory, or non-typical. The rather orderly development of pubic and axillary hair, the enlargement of the genitalia in both boys and girls, the enlargement of breasts, especially in girls, and the acceleration of all growth are some of the *sine qua non* of adolescence. On the other hand, there are certain non-obligatory physical developmental signs that the adolescent may have, such as, acne, seborrhea, possibly an increase in dental caries and gingivitis, obesity, and the development of colored striae. Perhaps more characteristic than any single one of these developmental changes is their variability or the degree to which they may appear.

One recognizes that an understanding of the physiology, the bio-chemistry, and the behavior manifestations of this period present a real challenge. It seems essential that those studying this period should first be familiar with the physical stigmata of youth. For the most part, our discussion will be confined to two frequently noted non-obligatory signs: the development of excessive adipose tissue, or obesity, and the frequent occurrence of colored striae.

Normal adolescents in some respects present difficulties for clinical study. As a group they are resistant to authority, especially parental; they are struggling for their identity; they demand the society of their age group; and they have many more interesting things to do than to see the "doctor." Some of them seem rather modest and may resent a complete physical examination.

Although one's private practice may afford good opportunity for longitudinal study of the teenage period, the number of children one sees is limited: adolescents just do not like to go to the doctor unless they have a serious health problem. In addition to the adolescents seen in private practice, we had an opportunity to study children in the Forsyth Dental Infirmary for Children. Here we have made detailed studies on all orthodontic patients (ca. 150), who are seen each year for many years. Most of

these children either desire or have been persuaded by their parents that orthodontic treatment is indicated, and thus long term studies are easily possible. By virtue of the fact that they are being studied or receiving treatment at relatively frequent intervals for long periods, excellent cooperation is assured.

It may seem unnecessary to state that all of our children are completely undressed for their examinations. This point is stressed here because in most of our school examinations children are only partially undressed, and in some of our best studies on growth and development, adolescents are dressed with special attire for examination. One cannot study these children thoroughly and be sure of seeing striae unless they are completely undressed.

In a group of 200 children who presented themselves consecutively for orthodontic treatment we designated 40 (or 20 per cent) who were in our opinion obese. This figure is not regarded as too significant because of the somewhat selective material and because there were many more girls than boys coming for orthodontic treatment. Most of these obese adolescents had fat pads and all were much above the expected weight. In contradistinction to so-called stout children, these boys and girls were unable to engage successfully in simple sports with their contemporaries.

The following case records are illustrations of obesity occurring in the adolescent period.

N. H. was first seen about three years ago, at 7 years of age, because her mother considered her too fat. She had always been a fat child, but had gained 8 pounds last year and 18 pounds the previous year. Although she was seen by various physicians for her obesity, only temporary success in weight reduction had been attained by a low caloric diet and reducing pills (dextro-amphetamine).

Although her parents presented emotional problems, the child herself seemed reasonably well adjusted. One aunt was obese, but the parents were not.

As far as could be ascertained, the patient's history—except for her obesity—was irrelevant. There was no history of birth trauma. Judged from her walking, talking, and dentition, her development was well advanced for her age. Socially, she was immature, and she enjoyed considering herself a baby. She engaged in no strenous play. Her diet to us did not seem unusual, nor did her eating habits. Her total food intake was not high for her age or weight. Like the diets of so many children, 52 per cent of her food intake was refined carbohydrate and 59 per cent of her caloric intake was from carbohydrate; her protein intake was adequate, and her milk intake was not excessive. She habitually ate between meals.

The physical examination showed a very obese girl with numerous fat

pads. She had typical pink striae over the upper gluteal regions, bilaterally, early pubic hair, the first stage of breast development, a large clitoris, no axillary hair, and no acne. The other results of the examination were not noteworthy; she had normal blood pressure and normal laboratory findings. Her bone age was about two years advanced.

This child illustrates a somewhat young obese adolescent girl. It is to be regretted that steroid assays were not made at this time to be compared with later steroid levels. She is regarded as an adolescent because of her enlarged genitalia and the presence of pubic hair; this judgment is strengthened by the striae and obesity. This child has been followed every 6 months for over 3 years; at 10 years she is still obese, but is now following a normal pattern of social and scholastic development, and has gradually become more independent. No specific diet has been advised.

Another obese girl has been followed for thirty years and illustrates the dangers of unreasonable restriction of diet. At 11 years this girl was a markedly obese adolescent manifesting all the obligatory and non-obligatory signs and symptoms of this period of development. Many of the family were obese and the girl's mother was "conditioned" to obesity, although her daughter was in no way concerned. In this instance it seemed as if something drastic must be done. In my enthusiasm to solve the problem and alleviate the family's anxiety, a very carefully calculated diet was prescribed. It was based upon the expected weight and gave all the essential food constituents for proper growth and development. The diet was apparently a perfect success and pounds were lost during the first three weeks. One morning, the mother called me in great distress asking to see me immediately. An early appointment was arranged, and the mother told me the following story: The previous night the parents were out, and in their absence my patient called a drug store saying her mother wanted one quart of chocolate ice cream. It was delivered, and the little fat girl, having stolen money from a member of the family, paid for the ice cream and ate it. When the mother heard of this, she was greatly concerned. For the first time, so far as she knew, her daughter had not only stolen, but had been untruthful. The experience was revealing to mother and doctor; both had a deep feeling of guilt. The mother had discovered traits in her adolescent child that were previously unknown. The doctor knew too well that he had precipitated this behavior. This girl is now among many that we have followed for two to three decades. She remained fat for many years, and although periodically she lost weight, she was always obese. She is married and has children, but not until recently, at the age of 32, has she become a so-called normal looking woman. It has taken years of trial and error, but she has been able to control her habits of eating and now has no excess fat.

The treatment of obesity associated with adolescence is not a simple matter. As the causes of this condition are undoubtedly legion, by the same token there are different types of treatment to be considered for each individual child. In general, we feel that it is best not to make radical reducing suggestions to these fat adolescents. The cause of their obesity is often too obscure for us to decipher. One cannot expect a child to limit his diet or change his life at this mercurial age when television encourages brands of sweet coated cereals, when brothers and sisters are drinking soda pop, eating marshmallow sandwiches, and when father and mother do not set examples of good eating habits and continually offer suggestions which elicit resistance and stimulate the already rebellious adolescent to be more so. It is best to make no frontal attack upon the obesity of an adolescent until the time arrives when the adolescent wants help. The success of any scheme of treatment depends upon the timing, and the skilled counsellor will recognize the opportune moment to take the initiative. Far more harm than good will result from treatment not based upon an understanding of the individual adolescent. One may question whether any physical or psychic trauma will result from a few more weeks or months of excess fat at the teen age.

Until the patient is psychologically ready to accept dietary instructions, something can be accomplished by laying the groundwork in the home. First, one must educate the parents and develop an interest and understanding of the importance of the correct attitude and diet for the family as a whole. Engaging the father's cooperation at times is not an easy task. A second must for success is to teach the family the desirability of some sport which will increase their physical activities. It has been quite impressively shown that girls going to our public schools, especially the obese ones, just do not exercise. They frequently ride to school; they are too fat to be skilled in sports and cannot compete well; and unfortunately, athletic facilities, especially for girls, are too limited. Generally, with a little encouragement from the right source, activities can be increased. First, it may be some form of dancing, then walking to school, then camp until some proficiency in a sport has been attained.

Not every personality in the medical profession may appeal to the obese adolescent. Fortunately, in our clinic, a very chic nutritionist conducts a class each week in which she gives fundamental dietary instructions, coupled with advice upon personal appearance—how girls can become more presentable. This simple departure from the mundane has greatly improved our percentage of successes. It must be remembered that a large percentage of obese boys and girls will eventually assume a good nutritional state under their own power.

This is not a time to discuss the best diet for these young people; it

must be adequate in all food elements and enough for growth. It has been found that if all between meal eating except certain fruits was eliminated, no other measures may be necessary. Frequently, on the other hand, some low caloric food eaten between meals assuages hunger and may help to prevent excessive eating at meals. One thing cannot be too emphatically stated: "reducing pills," so-called, should never be used.

The presence of colored striae occurring during adolescence, like an excess of adipose tissue, although not a specific sign, must be regarded as a non-obligatory finding in the late period of maturation. Formerly, when one thought of these striae, they were regarded as an accompaniment of obesity and were called "stretch marks", or *striae cutes distensae*. It is now quite clear that they represent a hormonal response and are very commonly seen in the adolescent period, in Cushing's syndrome, in pregnancy, and after administration of cortisone.

These striae are not associated with any subjective symptoms, and as yet they have not been correlated with any specific emotional or physical change in adolescence. They seem to occur frequently at the time of the linear growth spurt, but this is not constant. Teenagers are occasionally brought to a physician because the pink lines are so colorful and extensive as to cause parental anxiety. The patient rarely, if ever, seems concerned and generally is not cognizant of the presence of striae.

The incidence of striae in adolescence has never been accurately deter-

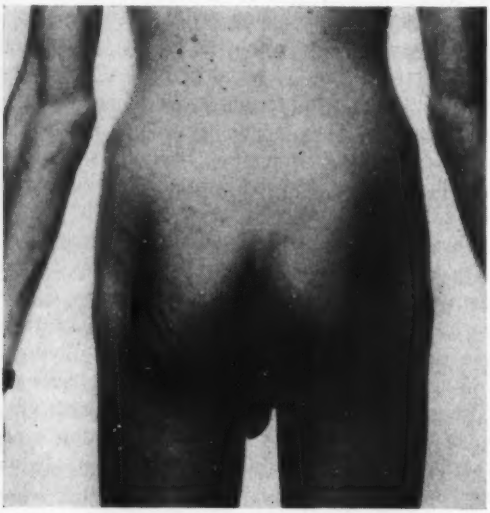

FIG. 1. Typical gluteal striae in a thin adolescent boy

FIG. 2. Extensive gluteal striae in a slightly obese adolescent girl

mined. In a study on growth and development at the Forsyth Dental Infirmary for Children in Boston, it was noted that striae were a very common finding. Later, during a study of the overall health of all orthodontic patients from 10 to 16 years of age, it was found that colored striae occurred in girls and boys with or without an excess of subcutaneous adipose tissue. In one group of 190 consecutive orthodontic children 67 (or 35.37 per cent) showed colored striae. In this group with colored striae there were 19 boys and 48 girls, or an incidence of 10 per cent in boys and 25.3 per cent in girls. More recently from longitudinal studies of children through their adolescent period, it appears that the occurrence of striae is extremely common. The colored striae can be easily missed, since they may be one of the earliest external manifestations of adolescence.

The distribution of the colored striae varies greatly. In general they are

FIG. 3. A drawing of striae showing elevation and pattern

located over the gluteal region. In some children one sees a few purplish lines at the crest of the ilium; in others the entire gluteal region will be delineated by the markings. At times they literally encircle the upper third of the thigh. A second common site for striae in girls is the breasts, and here also there is extreme variation in their appearance. At times they appear as a few wavy violaceous lines starting at the edge of the pigmented areola and extending down over the mammary gland, while they may appear also as prominent lines over the entire gland. In some very obese girls colored striae have been noted over the lower lumbar regions arranged horizontally, also over the lower abdomen and rarely over the upper arms.

It has now been possible to observe the early pink to purplish striae gradually change to a fine white line resembling a scar from an incision. These terminal stages of the colored striae may be difficult to detect unless the skin is stretched taut over the conventional sites.

The pattern and size of the striae also show great variation. Frequently they appear in a pattern of somewhat parallel lines with a slightly tortuous appearance. In size they may be 1–2 mm. and rarely much wider. In many instances the early larger striae are distinctly palpable.

In any discussion of adolescent striae, reference should be made to the association of striae with other recognized physical signs of this developmental period. It has already been pointed out that striae are frequently associated with obesity, especially in adolescent girls; but obesity is a non-obligatory sign of adolescence and striae are also very common in thin subjects. There are many boys and girls in our series who have been followed from early childhood through adolescence whose weight charts show no deviation from the expected and who clinically are regarded as normal who have typical adolescent striae in all stages. The common association of striae and obesity suggests there is some factor other than a mechanical one. This factor may be resolved by longitudinal steroid assays in teenagers.

Striae in general are associated with all the recognized external signs of adolescence, obligatory and non-obligatory. Occasionally we have seen colored striae appear before the development of pubic hair. They are common before the development of axillary hair and more common in the later stages of adolescence in both sexes. They are also associated with acne, but this condition, like obesity, is not always associated with colored striae.

The exact cause of these lesions of the skin in adolescence is not clearly understood. It is our opinion that, just as the growth and reddening of the cock's comb is produced by a hormone, the striae are probably associated with adrenal cortical activity. One cannot state categorically that there is not a mechanical factor associated with the formation of colored striae, but one can unequivocally state that this mechanical factor is not due to so-called stretching of the skin by deposition of excessive adipose tissue. Normal cleavages in the skin pattern, together with tensions from physical activities, may be regarded as possible contributory factors.

In summary, attention has been called especially to two clinical manifestations in the period called adolescence—the period of youth. No attempt has been made to give a comprehensive detailed account of all the changes that take place in this period. It is suggested that a knowledge of the physical changes in this period of rapid growth should be helpful in understanding the physiological and behavior pattern of the adolescent.

The signs of this growth period have been referred to as obligatory and non-obligatory. The fairly orderly development of linear growth, of pubic and axillary hair, of breasts and genitalia are illustrations of the former.

Two of the common non-obligatory changes, namely obesity and colored striae, have been discussed in detail. It is felt that obesity in the teenager presents a major problem in many instances, and since there are various causes for it, there are many types of treatment, and each obese adolescent requires individual study and care. At this time it is felt that colored striae are a non-obligatory sign of adolescence and are not due to a mechanical factor *per se*.

JUVENILE RHEUMATOID ARTHRITIS

Alvin Goldman, M.D.*
F. R. Leyva, M.D.†

Juvenile rheumatoid arthritis is a form of chronic polyarthritis occurring in childhood. Characteristically there is an insidious onset of a slowly progressing, painful stiffness and swelling of the joints accompanied by muscular atrophy and retarded growth. The joints during acute exacerbation are swollen, red and tender. When the disease is further characterized by generalized lymphadenopathy, splenomegaly and a general systemic reaction in the form of fever, malaise and weakness, it may be called Still's disease. In long standing cases the liver may be enlarged and amyloidosis may develop. The blood count usually shows a moderate anemia. Radiological changes are usually progressive. The joint spaces are slightly widened in the early stages and later there is a roughening of the joint margins with formation of bony spicules and eventually there is a rarefaction and ground glass appearance of the trabeculated ends of the bones. The joint spaces eventually become obliterated as the bones fuse.

The following is a report of a case of Still's disease, followed by a discussion of the pathogenesis and clinical aspects and supplemented with a description of a specific serological test for the diagnosis of this disease.

CASE REPORT

A 4½ year old colored girl was admitted to the Children's Hospital December 1, 1955 with the chief complaint of swelling and pain in the left elbow and right knee which had appeared intermittently since the age of 2 years.

The patient was born in Washington, D. C., March 1951, after a normal full term pregnancy, normal labor and spontaneous delivery. Her birth weight was 6 pounds. She was breast fed until the age of 5 months, and subsequently was fed whole milk and cereal. Because she was thought to be allergic to whole milk, sugar, oranges, apples, and bananas, her mother tried to avoid feeding her these. A typical breakfast included grits, bacon and eggs and a typical dinner included potatoes, greens, and liver. Her development was average.

Routine immunizations were incomplete and she had not been vaccinated.

Past illnesses included rubeola and varicella. There was no history of any injuries or surgery.

Her father was aged 29 and in good health. Her mother, 22 years of age, has hay fever and is allergic to apples, oranges and milk. There was no positive family history of rheumatic diseases, diabetes, syphilis, renal, cardiac, mental or malignant diseases. A paternal aunt had tuberculosis but was out of contact with the patient.

The patient's illness began when she was 2 years of age. At that time she was known to have had a mild traumatic injury to the right hand. When seen in the Out Patient Department her right hand was normal but both wrists were reported as swollen and tender with restricted movement to both. X-rays were ordered but not taken. Since that initial episode the patient had had several intermittent acute

* Former Resident.
† Associate Medical Staff.

exacerbations of tender, swollen, red joints, localized either in the left wrist, left elbow, or right knee with the most severe reaction appearing in the left elbow. She had been seen several times in the clinic of another hospital where x-rays were made. However, the patient's mother was informed that the films were normal. It was thought by the mother that the child was allergic to bananas, apples, oranges, sugar and milk and that following the ingestion of these foods an acute exacerbation of joint manifestation occurred, commencing with an associated appearance of a raised, erythematous, pruritic rash over the body which was thought to resemble measles. Subsequent to this the patient would develop abdominal cramps, loose bowel movements which were flecked with bright red blood and a prolapse of the rectum. The diarrheal state usually persisted for about one week. Although the joint involvement occurred through the year, the pain was most severe during the winter months. There was no history of trauma to the joints (except for the initial episode in the right hand), epistaxis, sore throats, chorea, nodule formation, carditis, or significant temperature elevation.

The present episode began one month prior to admission with the complaint of pain in the left elbow. This pain was accompanied by fever and warmth, redness and marked swelling. The pain gradually subsided but swelling became more marked. Two days prior to admission the patient ate some milk and cereal. The patient awakened during the night complaining of pain in the right knee; the knee was noted to be swollen, red, hot, and tender to palpation. The mother did not know if the patient had recently ingested any of her list of "allergic" foods. The child was brought to a private physician who advised her to be seen in the Out Patient Department.

On physical examination she was a small, asthenic, somewhat malnourished looking 4 year old colored girl in no acute distress. Her temperature was 101°, pulse 136 (reg.) respirations 26, weight 29½ pounds. Her blood pressure varied between 85/55 and 90/65. The skin was warm, dry, rough with several small areas of increased pigmentation on the trunk and extremities. A large scaly depigmented patch was present in the area of the left lateral thigh. Her head was symmetrical and appeared normal except for a circumscribed alopecic patch in the left anterior parietal region which was scaly, contained a few small raised areas oozing with thin sanguino-purulent material. The eyes, ears and throat were normal. The nose was congested and a mucopurulent discharge was present. The mouth appeared free of any lesions. The neck was supple. The chest was symmetrical. The heart was questionably enlarged to the left. The rhythm was normal and the rate 136. A systolic murmur of Grade I–II intensity was heard in the aortic and pulmonary areas and at Erb's point. The lungs were normal. The abdomen was soft and slightly protuberant; the liver edge was palpable 12 cm. below the right costal margin. The spleen was palpable 3 cm. below the left costal margin. No hernias were noted and there was no tenderness to palpation. There was no costo-vertebral angle tenderness and the external genitalia appeared normal. Rectal examination revealed flabbiness of the sphincter muscle with prolapse of the rectum on pushing down. There was no external change in the musculo-skeletal system. The left elbow and right knee were markedly swollen and appeared red and felt warm. Both were tender to palpation. Movements were restricted. Enlarged discrete and non tender lymph nodes were palpable in the cervical, axillary (larger in the left side), and inguinal regions.

Initial laboratory studies included:

Blood studies: Hemoglobin 6.6 gms. per 100 ml., erythrocytes 2,780,000, hematocrit 27 per cent, leukocytes 12,150 with 36 per cent segmented forms, 53 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophiles, platelets 500,000;

moderate hypochromia and slight anisocytosis; total eosinophiles 10 per cu. mm; sedimentation rate 40 mm per hour; no sickling noted.

Urinanalysis: Normal; serological test for syphilis, non-reactive.

Repeat blood studies one and two weeks after admission: hemoglobin 7.5 and 8.2 gms. per 100 ml. respectively, leukocytes 8,800 and 9,000 with normal differential; erythrocytes 4,020,000, and platelets 350,000.

Serial weekly sedimentation rates after the initial result were 36 and 39 mm. per hour respectively. On admission blood C-reactive protein was 4 plus and antistreptolysin "O" titer 833 units. Blood chemistry studies included: total protein 8.5, albumin 4.0, globulin 4.5 gm. per 100 ml; phosphorus 6.4 and calcium 11.1 mg per 100 ml. Blood cultures on three occasions were sterile. Throat culture showed alpha hemolytic streptococci. Exudate from a scalp lesion grew out *staphylococcus aureus*. A repeat antistreptolysin titer 12 days after admission was 500 units and the C-reactive protein was 3 plus. Lupus erythematosis cells were not found. A bone marrow biopsy was interpreted as showing an increase in the number of megakaryocytes and a marked increase in platelets. The red cells showed a moderate degree of polychromasia and there were occasional target cells. The leukocyte and erythrocytic series were unremarkable. The Leukoid:Erythroid ratio was 3:1. A muscle biopsy was reported as showing normal striated muscle and normal blood vessels.

X-rays: The cardiac silhouette and the lung parenchyma appeared normal. The liver and spleen appeared enlarged. The left upper extremity showed increased wasting with demineralization of all the structures. There were only 4 ossification centers for the carpal bones on the left as opposed to 6 on the right and the metacarpal centers were relatively smaller on the left side. There was cortical thickening of the proximal heads of the ulna and radius and of the distal part of the humerus. Necrosis was noted in the distal head of the left humerus. There was a swelling of the soft tissue around the right knee joint. There was no evidence of pathology in the pelvis, hips and upper portions of the femurs. The skull in all views appeared normal.

Electrocardiogram: Within normal limits for age and rate but slightly suggestive of right ventricular hypertrophy.

A sheep cell agglutination test for rheumatoid arthritis was performed on the patient's serum and was reported as positive at 1:16 and 1:32 dilutions which was interpreted as suggestive.

While in the hospital the patient was treated with a high caloric, high protein diet supplemented with multivitamins and a hematinic. She ate well and seemed to do well psychologically except during the periods after her mother left at the close of visiting hour when she cried bitterly, withdrew to herself. She was ambulatory most of the time and during her last week of hospitalization had daily occupational therapy.

A few days after her admission she was started on physiotherapy in an effort to improve the movement of the left elbow and arm. At the time of discharge the joint appeared vastly improved and there was only a minor amount of restriction of its use. The child was discharged on December 20, 1955 on a high caloric diet, multivitamins, a hematinic, instructions for physiotherapy for home care of her arm and asked to return to the medical clinic for a re-check in 3 weeks. She was also requested to be followed in the Allergy Clinic for investigation of any allergic component of her disease.

The patient was seen in the Medical Clinic on January 16, 1956. Her weight at that time was 32½ pounds, 3 pounds heavier than her weight on admission and ½ pound more than on discharge from the hospital. She had been doing well at home, eating satisfactorily and playing happily with the other children. Her left elbow

gave her very little trouble. Although still somewhat swollen she had very little restricted movement. She also ate all foods without any appearance of allergic manifestations.

On physical examination there were palpable cervical, axillary, and inguinal nodes. The liver was palpable 4–5 cm. below the right costal margin and the spleen was palpable 3 cm. below the left costal margin. The heart and lungs sounded normal. There were no restrictive movements of any of the joints but the left elbow was moderately swollen and the right knee slightly swollen.

Blood studies: Hemoglobin 8.9 per 100 ml., leukocytes 6,400, with 15 per cent segmented forms, 2 per cent bands, 76 lymphocytes, 6 per cent monocytes, and 1 per cent eosinophils; platelets normal; hematocrit 35 per cent; marked hypochromia and anisocytosis; few target cells; sedimentation rate 39 mm; sheep cell agglutination test for rheumatoid arthritis 1:4.

She was discharged and asked to return with the beginning of any acute symptom.

F. R. Leyva, M.D.

Juvenile rheumatoid arthritis is rheumatoid arthritis with onset prior to puberty. It may begin as early as one year of age, but the peak ages of onset are at three and between eight and eleven years.

The nature of onset varies considerably, from the more frequent insidious form to the fulminating febrile type. The insidious form is heralded by fatigue, low grade fever, pain and stiffness in one or more joints. I have seen children with monoarticular involvement for several months before other joints became affected by the process. However, more commonly there is a rapid progressive involvement of the joints with pain, swelling, stiffness and disability. Marked muscle wasting and flexion deformity are not long in appearing. In children the distal interphalangeal joints are commonly involved. The dorsal and lumbar spine and sacroiliac joint involvement are extremely rare in children but the involvement of the cervical spine is almost specific in the juvenile type. The clinical course of this insidious type is unpredictable. In many cases the active process terminates after a few months (3–6). The disease may remain inactive for many months or even years and then may reappear. In general, the course is one of repeated bouts of activity with long intervals of quiescence of years duration. The degree of disability varies considerably, although most cases maintain a fairly stable functional state.

The acute, explosive, type of rheumatoid arthritis is well exemplified in most cases of so-called Still's disease. These children usually have an abrupt onset of very high spiking fever that may remain for days or weeks as the only outstanding symptom. This fever usually is associated with frequent chills and *"profuse perspiration"* resembling a malarial attack. Shortly thereafter an abrupt onset of polyarthritis develops with swelling and intense marked pain of the joints, leukocytosis, elevated sedimentation rate and generalized lymphadenopathy. On occasion one sees pleurisy, pericarditis, splenomegaly and abdominal pain. These forms are very difficult

to differentiate from acute rheumatic fever during the first few weeks of the disease. However, the finding of low antistreptolysin "O" titer or a positive sheep cell agglutination test would help to establish the correct diagnosis. This acute phase may persist for many weeks and then subside entirely or may revert to a milder form of activity. However, some cases continue a progressive course with severe systemic manifestations; intermittent fever, marked wasting (cachexia), atrophic joint changes and interference with normal growth due to epiphysial involvement. Visceromegaly and finally amyloidosis and death may supervene.

So-called Still's disease or severe type of juvenile rheumatoid arthritis makes up about 20–25 per cent of all cases of rheumatoid arthritis in children. The prognosis before the steroid era was consistently poor and those surviving were usually greatly crippled. At the present time, based on recent information, it may be roughly said that 40 per cent of all cases obtain a good functional recovery, 40 per cent remain incapacitated and 20 per cent die.

The differential diagnosis of juvenile rheumatoid arthritis should include rheumatic fever, tuberculosis (particularly in monoarticular types), leukemia, infectious arthritis and traumatic arthritis.

The management of these patients still is a vexing problem because of differences of opinion. The idea of reserving hormonal therapy only for advanced cases in which other forms of treatment have failed seems somewhat illogical. Precisely, it is in these patients with advanced disease of more than three years duration in which hormonal therapy is unsatisfactory, due to irreversible tissue changes.

It seems reasonable that steroid therapy should be used early in patients with a moderately severe and progressive course. In the acute fulminating forms of rheumatoid arthritis vigorous steroid therapy is indicated. There is no doubt that you can maintain children on continuous effective low dosage of steroids, preferrably prednisone or prednisolone without developing clinical symptoms of hypercorticism or serious side effects. Again, it should be emphasized that these hormones do not alter the natural course of the disease. They suppress the systemic manifestations of the disease and this may prevent further injury to the tissues and may avoid subsequent deformities and disability.

Ed. note: The following article summarizes Dr. William's discussion of the application of the sheep cell agglutinin tests to the case reported in preceding pages.

SHEEP CELL AGGLUTININS IN RHEUMATOID ARTHRITIS

R. R. Williams, M.D.*

The sensitized sheep erythrocyte agglutination test in rheumatoid arthritis stems from the observation by Cecil and his associates that many strains of streptococci were agglutinated by the serum of patients with rheumatoid arthritis. Waaler in 1940 and Rose 1948, observed the agglutination of sheep cells sensitized with rabbit antiserum but found the incidence of positive tests low (33–37 per cent). Ball, Heller and Ziff have independently contributed to the diagnostic precision of the test and have variously reported 50, 70 and 85 per cent positive agglutinations in serum from patients with known rheumatoid arthritis. Serum from two to five per cent of people without evidence or history of rheumatoid arthritis have given positive agglutinations.

The test essentially consists of adding step-wise dilutions of serum to a sheep cell suspension containing sheep cell antibody at a concentration insufficient to agglutinate the cells. The serum of rheumatoid patients agglutinates these in higher titre than does the serum of non-rheumatoid patients. At the present time we consider a titre of 1:32 diagnostic and 1:16 strongly suggestive. The basis for this is, however, entirely statistical.

Several modifications are in use but vary only in amboceptor concentration used, per cent sheep cell suspension and method of reading. Ziff introduced the testing of euglobulin fractions to eliminate inhibitory substances present in all normal and in many rheumatoid arthritic serums. These inhibitory substances are found in Cohn's Fraction II which consists mainly of gamma globulins and contains antibodies and several other proteins. The agglutinating factor appears to occur in Cohn's Fraction III which is predominantly a beta globulin fraction but contains appreciable amounts of alpha and gamma globulins.

Clinically, the test has some useful and some rather discouraging characteristics for use in diagnosis and treatment. It is predominantly positive in patients who have had the disease for one year or more. A few cases have shown positive tests as early as six weeks from the clinical onset of disease, but these are exceptional. The titer is almost unaffected by treatment with salicylates, cortisone, or butazolidine, so it cannot be used to gauge remission. Concomitant disease such as psoriasis and a variant of rheumatoid arthritis, Marie-Strumpell spondylitis, almost always show negative agglu-

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tination tests. The collagen diseases, particularly lupus erythematosus disseminata, give a higher incidence of positive tests than does the general population. However, a positive test is only rarely seen in rheumatic fever.

In juvenile rheumatoid arthritis most of the same clinical principles hold in relation to the agglutination test. Positive tests are rarely seen early and the incidence in several small series has not exceeded 50 per cent positive tests. In the patient under discussion a suggestively positive test of 1:16 was obtained six weeks after onset of the disease, but a repeat test one month later was 1:4 which is considered negative. It will be of interest to follow her with serial tests if possible. At present one cannot make the diagnosis on the basis of the sheep cell agglutination. Possibly, in retrospect it will be possible to do so.

JUVENILE RHEUMATOID ARTHRITIS

A Review of the Literature*

Henry G. Cramblett, M.D.†

It has been almost one hundred years since Cornil[1] first described the occurrence of chronic arthritis in children. He did not speculate on its similarities or possible relationship to arthritis in adults. In 1897, Still[2] first described fourteen cases of rheumatoid arthritis occurring in children. He reported only the more severe forms of the condition. His cases were ones with severe systemic manifestations including lymphadenopathy, splenomegaly, anemia, adhesive pericarditis, and other visceral lesions associated with a severe, often crippling, arthritis. Thus, the idea was instilled in the minds of clinicians that juvenile rheumatoid arthritis is a rare disease, with an unfavorable prognosis, static in course, and largely intractable to therapy. Later on, it was recognized that the disease did exist in a milder form and this type was simply termed "childhood rheumatoid arthritis". Because of the frequent misuse of the name, Still's disease, to denote any case of rheumatoid arthritis in children, the American Rheumatism Association has advocated that the name "juvenile rheumatoid arthritis" be applied to all cases regardless of severity. Others have advocated that it be called "rheumatic disease". The latter name was proposed to emphasize that the disease is systemic in nature, although the arthritis has always

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attracted the most attention, and concentration on this single manifestation has certainly hampered the search for the cause of the disease.[3] In 1937, a rational challenge was given to the melancholy viewpoint of older clinicians regarding the disease when Colver[4] established that the disease had a much better prognosis than was formerly thought.

As now defined then, juvenile rheumatoid arthritis is a chronic disease of children, systemic in nature, nonspecific in cause, which almost invariably affects the joints by causing persistent changes in the synovia and secondary detrimental effects on the cartilages, ligaments, and musculature of the joints involved.

The disease in children is said to have its onset most frequently between the ages of two and four.[5, 6] Girls are affected more frequently than boys in a ratio of between 1.5 to 5 girls to 1 boy.[5, 7] The disease is not nearly so common in children as it is in adults. Approximately 4.9 per cent of all cases of rheumatoid arthritis seen at the Columbia Presbyterian Medical Center occurred in children.[5] In another series, 4.17 per cent of 314 cases of rheumatoid arthritis requiring hospitalization were in children all of whom had had their initial attack before the age of twelve.[4]

In another report, the incidence of patients with juvenile rheumatoid arthritis admitted to a large children's hospital in the period 1937 to 1949 was found to be 0.02 per cent.[8] However, there are definite indications that the disease is being diagnosed more frequently in its milder states now than in the past.

In from 20 per cent in Barkin's series to 32 per cent in Coss' series, a family history of possibly related conditions was elicited. The disease is one which occurs predominantly in the temperate climate.[9]

ETIOLOGY

The etiology of the disease is as yet unknown. Many observers have attempted to tie in so-called precipitating factors in order to explain the pathogenesis of the disease. The factor of preceding infection has been the center of considerable interest. Coss, in 1946, reported a series in which the streptococcal agglutination reaction was negative in thirty-two of thirty-five cases. This was in sharp disagreement with earlier reports.[5] He, however, stressed the importance of antistreptolysin titers which in his series had a high median of 250. This was considered to be elevated and to be almost certain evidence of recent streptococcal infection. It should be emphasized that a rise in the titer during the illness was not demonstrated. Coss felt that in his series he had found some relationship to mild respiratory infections which were followed by a lag period of three to ten weeks before the development of joint symptoms. This was in accord with Rich's idea that the lesions of rheumatoid arthritis may be due not to the direct

action of a bacterial toxin per se, but may represent the effect of a hypersensitive reaction to bacterial products.[10] Kalbak, on the other hand, along with other observers has shown the agglutination studies against the Group A hemolytic streptococcus to be positive in 50 per cent to 80 per cent of adult patients with rheumatoid arthritis.[11]

The editors of a recent review on rheumatism and arthritis feel that it has been fairly clearly shown that the antistreptolysin and streptococcal antihyaluronidase titers are for the most part normal in patients with rheumatoid arthritis.[12] This contradicts the earlier mentioned report that the antistreptolysin titer was elevated in this disease. It is now felt that a markedly elevated or rising antistreptolysin titer in a child with joint disease is strong evidence against the diagnosis of rheumatoid arthritis. Generally then, the absence of significant antibody titers against streptococcal products in patients with rheumatoid arthritis does not lend support to the hypothesis that the hemolytic streptococcus is the etiologic factor in rheumatoid arthritis.[12]

The factor of hypersensitivity has also long been considered in the pathogenesis of rheumatoid arthritis. The increase in gamma globulin demonstrated by electrophoretic and immunologic measurements has been assumed to reflect antibody production although the responsible antigen or antigens are as yet unknown.[13] In more recent studies, the removal of specific streptococcus agglutinins did not alter the electrophoretic pattern of rheumatoid arthritis serum, and there was no apparent correlation between gamma globulin concentration in plasma and the titers of streptococcus agglutinins, of antistreptolysins or of differential agglutinins of sheep red cells.[12] The substance responsible for the agglutination of sensitized sheep cells was localized in the globulin fraction of the serum, but it was not directly associated with streptococcus agglutinins or with factors responsible for alterations in erythrocyte sedimentation rate.

Wallis[14] has theorized that the antigen responsible for excessive antibody production in rheumatoid arthritis is a by-product of the synovial cell. He suggested that the pathogenesis of rheumatoid arthritis is based on the effects of fixation of antibodies by tissues in the smooth muscle walls of arterioles. As a result of this antibody fixation, a metabolite of arteriolar smooth muscle action interferes with synthesis of hyaluronic acid by synovial cells, "leading to the production of two abnormal substances, one an irritant responsible for the patient's symptoms and the other an antigen which by arousing antibodies completes a vicious circle whereby the disease perpetuates itself".[14] This hypothesis appears complicated and does not readily suggest avenues by which it may be tested experimentally.

The factors of altered metabolism and of altered nutrition have also been mentioned in discussions of the etiology of the disease. There is no evidence

at present that either of these bears any direct relationship to the pathogenesis of this disorder.

The fact alone that the symptoms of rheumatoid arthritis respond so well to hormonal therapy suggests that there might be some endocrine imbalance. In nine of ten autopsied cases of active rheumatoid arthritis, and in one of three cases of lupus erythematosus disseminatus, identical abnormalities of the pituitary glands were observed.[15] These consisted of a selective degranulation of the mucoid cells (basophils, cyanophils) similar to that seen in Addison's disease but not found among the two hundred controls. These alterations, allegedly specific, were considered to be secondary to dysfunction of the adrenal gland. An abnormality in metabolism of cortisone in affected tissues in rheumatoid arthritis rather than a deficient production of this hormone has been suggested because of the high dosage level required for relief of symptoms, as well as by the absence of recognizable evidences of adrenal insufficiency.

There has been an attempt to associate the pleuropneumonia-like organisms with the etiology of rheumatoid arthritis.[16] Such organisms were isolated from the joint fluid of two patients with arthritis. However, in both cases, there was associated genito-urinary tract disease. The present evidence is certainly inconclusive that these organisms play any part in the etiology of rheumatoid arthritis.

There are still many who feel that trauma, autonomic imbalance, and psychogenic factors play important etiologic roles.

PATHOLOGY

The pathological changes in rheumatoid arthritis are widespread, involving a variety of organs and tissues, but predominantly the connective tissues. Often the histopathology is relatively specific, characterized by both degeneration and proliferation. Weber[17] refers to these changes as necrobiosis, that is, "what goes on in a part when a degenerative necrotic focus is opposed by a vital reactionary process of repair and regeneration". This is best seen in the subcutaneous nodule but may also be observed in other areas. The nodule, itself, is specific and contains three distinct zones: (1) a central area of necrosis, (2) an intermediate zone of fibroblasts in palisade arrangement, and (3) a peripheral zone of cellular infiltration (largely lymphocytes and plasma cells) which merges into the surrounding connective tissue. These nodules occur in 10 per cent to 20 per cent of cases and are generally found where pressure and trauma may most easily impinge on bony prominences.[18]

The articular lesions are the best known and in the past have received the most attention. In the encapsulating membrane, one sees successive changes of hypertrophy of the endothelial cells, increased vascularization,

cellular infiltration, accumulation of inflammatory cells in follicle-like collections and pannus formation which grows in and about the articular surfaces. The cartilage articulation is involved only passively, being destroyed by the ingrowing pannus with erosion, pitting and fraying of the surfaces. The epiphyseal bone is also affected in the pathological process. Osteoporosis with greater fragility of the bone and also widening of the joint spaces with increased fat are not uncommonly seen. Granulations and follicle-like accumulations of lymphocytes in the marrow spaces are often present. These are postulated by many to have a part in the destruction of the subchondral bone which does occur. Osteoid formation within the subchondral granulations leading to eventual bone production explains the formation of the so-called spurs. Erosion with absorption and disappearance of bone in the region of the articulations or beneath the subchondral plate frequently is observed. Eburnation or marbling of bone in the area of the subchondral plate is found where the overlying cartilage has been destroyed. As the disease becomes chronic, there is marked narrowing of the joint spaces, and bony ankylosis may occur.

The lesions of rheumatoid spondylitis have not received much attention until recently when Barkin[19] reported that of seventy-one children with rheumatoid arthritis, 80 per cent had either x-ray or clinical evidence of spondylitis. In 70 per cent, x-ray changes were demonstrable. The radiological picture is the same as that observed elsewhere, i.e., narrowing, irregularity and often fusion of the apophyses. In contradistinction to Marie-Strümpell's disease, the involvement is most commonly of the cervical spine.

Striated musculature may be affected both directly and indirectly. Atrophy secondary to joint involvement occurs quite commonly. Minute microscopic nodules composed of lymphocytes, plasma cells, epithelioid cells and eosinophiles may be seen within the muscle itself.

Peripheral nerves, tendons, sheaths, and bursae may similarly be affected by the type of nodule just described.[20, 21] Central nervous system involvement has long been suspected but not proved.

Of the numerous visceral lesions, the cardiac lesions have attracted the most attention. This is not surprising when one considers the difficulties that heart findings present in the differential diagnosis. Most of the available information in the literature deals with adults. It has long been known that heart lesions of various types are more frequent in patients with rheumatoid arthritis who come to autopsy than in a general series of post mortem examinations.[22, 23] As high as 42 per cent of patients dying with rheumatoid arthritis and coming to autopsy have been found to have cardiac inflammatory reactions indistinguishable from rheumatic fever. The actual unrelated presence of rheumatic fever could not be suggested by

history in any of these cases.[18] All grades of inflammation from acute to chronic with degenerating cardiac fibers, cellular infiltration, pericarditis, myocarditis, typical Aschoff bodies, and even nodules similar microscopically to the subcutaneous rheumatoid nodule have been found within the heart.

The observation has been made many times that the above described lesions were less diffuse and less severe than those usually seen in proved rheumatic heart disease.[12] On post mortem examination of forty-five cases of rheumatoid arthritis, mostly in adults, Bauer and Clark[24] described pericarditis in 44 per cent, one-half of which were associated with myocardial infarction or alterations more suggestive of rheumatic fever. Twenty per cent had gross valvular disease; mitral stenosis was present in 14 per cent, but in only one case could a definite diagnosis of rheumatic heart disease be made. It appears likely that certain alterations, then, especially those showing the histopathology of rheumatoid nodules and pericarditis, are additional systemic manifestations of rheumatoid arthritis.

Because of the cardiac lesions, it has been suggested that rheumatoid arthritis and rheumatic fever are closely related or even identical conditions.[25] Of course, there is no reason why both rheumatoid arthritis and rheumatic fever could not co-exist in the same patient.

The liver, lymph nodes, and spleen may be enlarged. Microscopically, there is reticulum cell hyperplasia and in the liver, there may be chronic passive congestion.[26]

There have been many reports in the literature concerning the occurrence of amyloid disease as a complication of rheumatoid arthritis.[27, 28] Moschcowitz[29] has postulated that rheumatoid arthritis, per se, does not cause amyloidosis but that the two diseases possibly represent a reaction to the same etiologic factor. Trasoff,[28] in 1944, suggested that many of the deaths in rheumatoid arthritis not coming to autopsy were due to the development of amyloid disease. Amyloidosis affects the kidneys most often and the liver and spleen less commonly. Amyloidosis should be suspected in patients with rheumatoid arthritis, if albuminuria is present and if the spleen and liver are enlarged. Liver or lymph node biopsy may aid in the diagnosis.

CLINICAL PICTURE

The diagnosis of juvenile rheumatoid arthritis may be a very difficult one to make. Only too often a mild attack may be regarded as a minor traumatic incident or labeled such descriptive terms as toxic, nonspecific, or villus synovitis. Rheumatoid arthritis frequently exists in children as a monoarticular disease and in overlooking this, clinicians tend to misdiagnose the case as tuberculosis. In addition, in the absence of definite substantiat-

ing evidence, there is a tendency to dismiss the monoarticular cases as instances of brucellosis, gonorrhea, or syphilis.[6] Then, too, it is often impossible in one examination to differentiate between rheumatic fever and rheumatoid arthritis.

Not uncommonly fever may be the earliest manifestation of rheumatoid arthritis. It may be persistent or intermittent in type and often spikes to 105 degrees.[30] Fever may be accompanied by other severe systemic manifestations with slow insidious onset including malaise, tachycardia, nosebleeds, weight loss, and migratory transient polyarthritis not unlike rheumatic fever. In general, the systemic symptoms in children are more severe than those seen in adults.

It may be several days to several weeks from the onset of symptoms before the joints become involved. The joints show signs of active inflammation including effusion, tenderness, increased heat, and muscle spasm. Redness is rare except in infants, and pain at rest is usually absent in the early stage. In children, the arthritis is not uncommonly monoarticular while this is rare in adults in whom it tends to be multiple and symmetrical. The large joints such as the knee, hip, and ankle are more frequently involved in children in contradistinction to the adult pattern of smaller joints being involved.[31] The joints do not tend to be hyperesthetic, but the pain may be severe with the slightest movement. The joints most commonly involved during the course of the illness arranged in order of decreasing frequency from a compilation of several reports include: the knee, hand, elbow, wrist, ankle, hip, shoulder, temporomandibular, cervical spine, foot and jaw.[4, 32, 7, 5] The knee is the joint most commonly involved initially.

Rashes of different varieties have been described as occurring in rheumatoid arthritis. The most common rash is said to be urticarial or maculopapular in type.[30] Erythema multiforme as well as petechial type skin lesions have been reported. The rash may be transitory and may be present only during febrile periods. Fever and transitory skin rashes may precede actual joint involvement as long as six months.[37]

Liver and splenic enlargement have been described as being present in as high as 23 per cent and 30 per cent of the cases respectively. In one series, the spleen was enlarged in 9 of 12 patients coming to autopsy.[26] Generalized lymph node involvement of some degree is said to be found in up to 60 per cent of patients with this disease.[5] Lymph node enlargement is seen more often in the younger patients.

Subcutaneous nodules occur in juvenile rheumatoid arthritis but not as frequently as they do in adults. From 12 per cent to 20 per cent will show them ordinarily; some series have reported an incidence of 30 per cent in patients followed for long periods of time.[4] Rheumatoid tenosynovitis occasionally is noted and may lead to palmar contractures.

The neuromuscular system is most certainly affected but the amount of direct involvement is not as yet known. It is true that one sees muscular weakness, atrophy, tremors, twitchings, numbness and paresthesias. Electromyographic studies have shown an inconstant state of tension at rest in patients with rheumatoid arthritis.[21]

Ocular manifestations are not at all uncommon in this disease. The triad of band shaped keratopathy, iritis, and juvenile rheumatoid arthritis has received special attention in the literature.[33a, 33b] In one series of 162 children, 21 per cent were found to have eye changes.[33b]

Cardiac signs have been reported as being present in as high as 47 per cent of cases. These findings are difficult to evaluate and cause a great deal of confusion in trying to make the diagnosis. It is commonly agreed that pericarditis does occur in rheumatoid arthritis along with other pathological findings already mentioned. In one series, five of twenty-one children with the disease were felt on clinical grounds to have pericardial involvement.[32] Tachycardia is frequently present. On the other hand, in one investigation, the results of ausculatory examination, roentgenograms of cardiac contour, and electrocardiograms were approximately the same in 147 adult patients with rheumatoid arthritis as in 100 carefully matched normal patients.[34] Studies of this kind would cause one to wonder whether some of the cases reported in the literature with marked cardiac involvement may not have been misdiagnosed cases of rheumatic fever.

Inflammation of serous surfaces other than the pericardium may occur. Pleuritis and peritonitis may be present. Interstitial pneumonitis with fibrinoid necrosis similar to that seen in other collagen disorders has been reported.[35]

Kuhns and Swain were among the first to notice the generalized inhibition of growth in rheumatoid arthritis. They also described several instances of deformities due to local epiphyseal inhibition of growth, causing such conditions as brachydactylia.[36] One of the most characteristic deformities occurs when the temporomandibular joint is affected as seen in 14 per cent to 17 per cent of cases.[37] Rheumatoid arthritis interferes with the proliferation of cartilage in the condylar head, the most active growing center in the jaw, and this results in a striking craniofacial dysplasia which may be best visualized with a laminogram.

Laboratory Data

Leukocytosis with a polymorphonuclear response may be quite prominent especially in younger children who have visceral involvement.[33] Thirty-seven per cent of cases in one series had white blood cell counts of between 15,000 and 25,000. Seventeen per cent had counts exceeding 25,000. The leukocytosis may be maintained for weeks or even months before falling to normal levels. Leukopenia following an initial leukocytosis is considered to

be a grave prognostic sign indicating an especially "malignant" form of the disease. As might be expected, in the acute forms, the bone marrow shows hyperplasia of the granulocytic series. However, not too rarely, the degree of hyperplasia fails to correspond to the peripheral count. A moderate anemia is seen in up to 80 per cent of reported cases.[5]

The anemia is normocytic hypochromic and is rarely severe. The reticulocyte level is usually near normal. The serum iron concentration may be decreased but the total iron-binding protein is within normal limits.[39]

The sedimentation rate is elevated and parallels rather well the clinical course of the disease. Because of this, it is a reliable gauge of activity. All attempts to correlate hyaluronic acid with the degree of sedimentation rate elevation have been unsuccessful in this disease.[40]

There is usually hypoalbuminemia associated with a moderate increase in the beta globulin and marked increases in gamma globulin. It is not uncommon to find the alpha globulins increased in the acute phase of the disease.[41] There is often an increased fibrinogen content. The return of the Tiselius pattern toward normal coincides with clinical improvement.

The x-ray may show no abnormality other than encapsulated synovial fluid for as long as six to eight months. Even then the abnormalities are not diagnostic. Osteoporosis sometimes develops early and may offer a hint as to the diagnosis, but this is certainly non-specific. Recently, subarticular pseudocysts have been described in adults with the disease.[42] They are seen at all stages during the course of rheumatoid arthritis. The characteristic findings in a typical advanced case include soft tissue swelling, decalcification, narrowing of joint spaces and bony ankylosis.

Examination of the joint fluid is very helpful in establishing the diagnosis of rheumatoid arthritis. It is especially useful in differentiating traumatic arthritis, in which case the inflammation is minimal and in which the synovial fluids show little variation from normal. Cultures of the fluid will rule out the septic types of arthritis and are especially helpful when the disease is monoarticular. The fluid in lupus erythematosus rarely contains over 3000 cells per cubic centimeter, and this may be an important distinguishing characteristic.

Grossly, the aspirated joint fluid in rheumatoid arthritis varies from clear to turbid. Its cell count averages 14,000 but may go as high as 66,000.[43] The normal cell count is 13 to 180. The fluid usually contains a preponderance of polymorphonuclear cells, on the average of about 65 per cent. Normal fluid contains up to 25 per cent. The total protein averages about 3 to 8.9 grams per cent compared with the upper limit of normal which is 2.1 grams per cent. The globulin which normally is 0.05 gram per cent ranges from 1.2 to 6.8 grams per cent in rheumatoid arthritis. Often an increased sugar differential between the joint fluid and the serum is

found. The mucin when precipitated with dilute acetic acid gives a loose friable precipitate as opposed to the tight ropey one found in normal fluid.

Another serological test has recently been described in which the sera from rheumatoid arthritis patients have been shown to agglutinate sensitized sheep red cells in much higher dilutions than does normal serum.[44] This was shown to parallel the clinical course of the disease, but not the response to cortisone. The substance responsible for this test is a globulin. It is not the same as the heterophile antibody found in infectious mononucleosis. The test does not become positive until several weeks after the onset of the disease, and there is evidence that the incidence of positive tests increases as the duration of the disease increases.[45]

Recently, it has been found that the serum of patients with rheumatoid arthritis has cold precipitable substances which are capable of agglutinating sensitized sheep erythrocytes. The authors feel that this is the basis for a diagnostic test much more reliable than the tests employing unfractionated serum. However, the agglutinating substance does not appear in the blood for at least two months.[46]

Patients with rheumatoid arthritis may show increased spinal fluid protein.[47, 48] This is especially true when there is spondylitis present.

Patients with this disease have also been reported to show an inability to handle orally administered glucose as demonstrated by impaired glucose tolerance tests.[25]

There has been increasing enthusiasm for performing synovial biopsies in the more troublesome diagnostic cases. The pathological findings are often specific enough to establish the diagnosis.[41, 49]

DIFFERENTIAL DIAGNOSIS

Rheumatoid arthritis may be confused with one of the specific infectious arthritides especially if the involvement is monoarticular. A negative tuberculin test helps to rule out tuberculosis, and the absence of specific agglutinins will help to dismiss brucellosis and enteric organisms as causes of the disease. Blood cultures and cultures of the joint fluid, if negative, will also aid in pointing to the diagnosis of rheumatoid arthritis. Syphilitic arthritis is rarely seen.

Rheumatic fever is the most difficult disease to discount in the differential. This is especially true since both may cause cardiac lesions. The prodromal period of the two diseases may be identical. The joint effusion in rheumatic fever is quite transient and rarely lasts more than a few days. The joints tend to be red in rheumatic fever while they rarely are in rheumatoid arthritis. In rheumatic fever, there is an antecedent history of upper respiratory infection or sore throat in 74 per cent of the cases, while this is true in only 9 per cent of the cases of rheumatoid arthritis.[59] There is quite

a dramatic response to the salicylates in rheumatic fever while this is not true ordinarily in rheumatoid arthritis. This serves as a valuable therapeutic-diagnostic test. A rising antistreptolysin titer is much in favor of rheumatic fever and may be diagnostic.

A surprisingly large number of patients with lupus erythematosus have arthralgia. Then, too, they may have pericarditis. However, the common renal involvement with albuminuria and hematuria along with a leukopenia and the finding of the "lupus-erythematosus" cell help to differentiate lupus from rheumatoid arthritis.

Anaphylactoid purpura (Henoch-Schoenlein's purpura) may also cause arthralgia. Here there may be widespread purpuric areas in the skin as well as hematuria which aid in the differential diagnosis.

Another condition that may be confused with rheumatoid arthritis is leukemia. This has been reported in the literature several times in the past and again only recently,[51] In the chronic forms of rheumatoid arthritis, one occasionally sees peripheral blood smears very suggestive of the more malignant disease. There has been speculation that rheumatoid arthritis may predispose to that disease.

Other conditions to be included in the differential are sarcoidosis, dermatomyositis, scleroderma, periarteritis nodosa and trauma.

PROGNOSIS

The prognosis of juvenile rheumatoid arthritis was considered very grave until 1937 when Colver indicated that many patients recover completely. In his original series of 69 patients, 12 died of various causes including pneumonia, septicemia, urinary tract infection, amyloidosis, and cachexia.[4] Seven of his patients recovered completely while twelve others were crippled but still had functional activity. The remaining patients were more severely affected. Of the ones that died, the disease, without exception had begun before the age of five, and they were all dead within three years of the beginning of the disease.

Pickard in 1947 reported a series of cases indicating an even better outlook. Forty per cent of his patients made a complete recovery.[6] Approximately 9 per cent of his patients died, and 14 per cent more were severely crippled. The remainder of the patients were crippled but had functional use of the involved parts.

In 1952, Barkin reported his experience with forty-five cases. Ten of his cases died after an average duration of the disease of thirteen years.[52] Twelve of his cases were of the severe type with visceral involvement. Seventy per cent of his group had moderate functional capacity. He still considers the disease one of prolonged or recurrent nature, with considerable mortality, low incidence of complete recovery, and with some degree

of functional impairment in almost all cases. His series may be criticized from a prognostic standpoint because his cases were all severely ill ones who had required hospitalization.

Richmond, also in 1952, published a series which agrees with Pickard's more optimistic report. He feels that over 40 per cent of the cases recover completely.[51]

In a more recent publication, Fyfe[53] reports on a group of patients followed from 1930 to present. In this series, 60.7 per cent have been quiescent for two years or more. Of this group, however, only about one-third have shown complete recovery. The rest of the patients have some degree of functional involvement. Of the remaining patients, 33.9 per cent have active disease and 5.4 per cent have died.

At one time, the view was commonly expressed that juvenile rheumatoid arthritis always underwent a spontaneous remission at puberty. This, however, has been disproved.

Generally speaking, it seems fair to estimate that approximately one-third of all patients will recover completely, another third will have some degree of functional incapacity, one-sixth will have severe residual deformities and another sixth will die as a result of their illness.

Treatment

The discovery by Hench, Kendall, and Reichstein that cortisone and corticotropin ameliorate the clinical aspects of rheumatoid arthritis gave much impetus to the study of the disease. At last, there was something that would give dramatic relief to the suffering caused by this prevalent condition. Just how cortisone and corticotropin bring about their effects is unknown. Their use was justified originally by the idea that in conditions where rheumatoid arthritis improved, that perhaps the liver's inability to detoxify these compounds and their subsequent accumulation might be an important factor. It was well known that hepatitis and biliary obstruction often led to an amelioration or actual cessation of symptoms from rheumatoid arthritis.[54] It was also noted that the disease was influenced favorably during pregnancy, in cases of febrile reactions due to foreign proteins, and, also, often in starvation.[55]

The response to these hormones is almost universal. Within a few hours to a maximum of four days, there is noted a marked decrease in muscular stiffness, joint pain, aching and tenderness.[56, 57] This is associated with increased range of motion of the joints. The constitutional symptoms improve likewise in that a sense of well being occurs, as well as increased appetite and weight gain. Fever, if present, disappears rapidly. There is usually little or no effect, however, on the sedimentation rate. The anemia and the lowered plasma proteins are improved. This may be related to

better nutrition. Maximal improvement usually occurs within one to three months.

The effects on the pathological processes are much less marked. It is true that articular biopsies in some cases have shown a lessening of the inflammation, but the process always remains even though it be in decreased intensity. There is no evidence that it ever has any influence upon the final crippling nature of the disease. In some cases, the clinical manifestations are decreased while the pathological processes of the disease advance.[58] Generally, then, there has been little objective benefit noted; the greatest benefits are due to amelioration of the symptoms.[59]

The British Medical Research Council under the chairmanship of Sir Henry Cohen reported in 1954 on a series of 61 adult patients with acute rheumatoid arthritis treated alternately with aspirin and cortisone.[30] The dosage was individualized in each case according to need. Observations were made on the patients at one week, eight weeks, thirteen weeks and one year after therapy was begun. It was clearly shown that the two groups ran a closely parallel course in all recorded characteristics—namely, joint tenderness, range of movement in the wrist, strength of grip, tests of dexterity of hand and foot, and clinical judgments of the activity of the disease and of the patient's functional capacity. The hemoglobin level and erythrocyte sedimentation rate were slightly more favorably influenced by cortisone.

As is the response to the hormones initially almost universal, so is the course following discontinuance of the medication. In most series, it was the rare case in which cessation of treatment did not result in an exacerbation of the disease, sometimes more severe than had been the case before treatment.[31]

Thus, before embarking upon a course of hormonal therapy in rheumatoid arthritis, one must remember that the benefits are temporary and suppressive only, not curative. The hormones must be given more or less continuously to maintain the benefits. Adverse hormonal complications often develop especially in children because of the relatively large dosages needed for effect. Refractoriness or escape from therapy is relatively frequent.

Corticotropin and cortisone may be indicated in those cases which are rapidly progressive with severe systemic manifestations for which simpler medications have been of no value, and especially those where the patient is threatened with death or severe disability.[58]

Analgesics should always be tried although they often do not afford much relief. Nothing surpasses acetylsalicylic acid alone. Attempts to prolong the action of this drug have been largely unsuccessful, although many prefer its combination with sodium paraminobenzoate.

The use of alternate rest and motion must be applied intelligently and

adapted to the individual case. The patient in most instances should not be completely immobilized, and complete bed rest is hardly, if ever, indicated, except perhaps in the acute febrile stage. As a matter of fact, there is a growing tendency toward early ambulation. Muscular atrophy, contractures, and ankyloses should be prevented by an intelligent regime of adequate posture and exercise. Splints worn for part of each day will prevent the insidious development of flexion contractures.

Diet and vitamins, especially Vitamin D, have not been shown to play any large part in the treatment. Excesses of Vitamin D have often caused severe poisoning. The diet, as in any chronic illness, should be adequate and nutritious.

The anemia, if present, should be corrected. The anemia does not respond to intravenous or oral iron, but cortisone has been reported to be beneficial.[39] Folic acid has been observed to be of values in some cases.

Psychotherapy to combat the anxiety and depression of the patient is always important as is true in the treatment of any chronic illness.

Treatment of foci of infection, vaccines, fever therapy, and roentgen therapy are modes of treatment that have had and still do have proponents. There is no direct evidence that these approaches have any effect upon the disease.

Many feel that chrysotherapy is still the best single mode of treatment.[60] In a study of seven thousand patients, it was found that sixty-one per cent were benefited; however, there was a relapse rate of 50 per cent to 80 per cent. The toxicity of the preparation is great and its use is considered to be quite dangerous. Toxic reactions have been reported in different series to be as high as 62 per cent.

Antispasmodics of different types have been used from time to time without too much in the way of convincing results. Neostigmine and physostigmine have come into rather wide usage, but their effects are short and of questionable value.

There have been several reports on the use of phenylbutazone (Butazolodin) in rheumatoid arthritis.[32, 61, 62, 63] While the symptoms are controlled in as high as 80 per cent of the cases, the drug is not curative.[62] It does have some anti-inflammatory effect. Toxic complications include water retention, rashes, stomatitis, and epigastric pain.[63]

The use of isoniazid in the treatment of this disease (in one case) was recently reported from Athens, Greece.[64] The drug was administered over a nine month period. During the first few months, there was a gradual improvement in the clinical condition but the sedimentation rate remained elevated and fever persisted. At the end of therapy the patient's condition had improved to the point that her X-rays were normal. Further clinical trials are needed to confirm the beneficial effects of this medication.

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